Synthesis of 1-Substituted and 1-Unsubstituted 4-Sulfonamido-1*H*-pyrazol-5(2*H*)-ones

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4-Sulfonamido-1*H*-pyrazol-5(2*H*)-ones bearing different substituent groups on the nitrogen atom in position 1 were easily obtained by reaction of conjugated azoalkenes with sulfonamides under mild conditions. 1-Unsubstituted title compounds were smoothly obtained by solvolytic cleavage of the substituent groups in methanol under reflux.

Sulfonamidic derivatives represent a class of organic compounds very important both from the synthetic and pharmaceutic (i.e. sulfamidic drugs and saccharin) point of view.[1] Considering this fact and the ability of conjugated azoalkenes to undergo nucleophilic attack to give pyrrole,[2a-c] pyrazole[2c] and thiazole rings,[3] we decided to investigate the reaction between these latter substrates and some sulfonamido reagents in order to tentatively synthesize the title compounds. These studies are generally aimed at demonstrating the versatility of conjugated azoalkenes as useful tools in organic synthesis especially in carbon functionalization, including carbon-carbon bond formation,[2a] and to show, in particular, that these compounds represent valuable starting materials in general strategies directed to the preparation of a variety of unknown polyfunctionalized heterocyclic rings.[2-4] Unlike the homodiene system in conjugated dienes, the presence of the azo group in the heterodiene system of conjugated azoalkenes is able to favour nucleophilic attack, as well as to make the same attack regioselective on the terminal carbon atom. The substituent effect of the groups (electron-rich or electron-poor) mainly located on the terminal carbon or nitrogen atoms of the azoene system[5] plays a considerable role in these reactions.

Conjugated amino- **1a–b**, phenylamino- **1c–d** or alkoxycarbonylazoalkenes **1e–h** react with *o*-benzoic sulfimide (saccharin, **2b**) or *N'*-(2-thiazolyl)sulfanilamide **(2c)** at room temperature in tetrahydrofuran within 0.2–48 h in the presence of a catalytic amount of sodium methoxide to give the hydrazine derivatives **3a–h, j–k** in excellent yields (82–97%) (Tables 1 and 2). The hydrazine derivatives **3a–h, j–k** likely originate by 1,4-conjugate addition (Michael-type) of the sulfonamido reagents, as a consequence of the nucleophilic attack by the amido group onto the terminal carbon atom of the heterodienic system of conjugated azoalkenes, producing hydrazono intermediates that rapidly tautomerize into the corresponding hydrazino forms. The treatment of the hydrazine derivatives **3a–h, j–k** with sodium hydride in methanol at room temperature (0.1–2 h) results in the production of the 1-substituted 4-sulfonamido-1*H*-pyrazol-5(2*H*)-ones **4c–h**, and **4j–k**. Since the reactions of conjugated azoalkenes **1a** and **1c** with *N*-methyl-*p*-toluenesulfonamide **(2a)** as well as between conjugated azoalkene **1d** and *N'*-(2-thiazolyl)sulfanilamide **(2c)**, provide not easily isolable intermediates, we preferred to carry out the preparation of pertinent 1-substituted 4-sulfonamido-1*H*-pyrazol-5(2*H*)-ones **4a–b** and **4i** directly by addition of sodium hydride to the reaction medium after the disappearance of the starting conjugated azoalkenes (Tables 3 and 4). 1-Substituted 4-sulfonamido-1*H*-pyrazol-5(2*H*)-ones **4a–g** in methanol under reflux within 2–6.5 h smoothly lead to the 1-unsubstituted 4-sulfonamido-1*H*-pyrazol-5(2*H*)-ones **5a–b** in good to excellent yields (76–89%) by solvolytic cleavage of the groups linked to nitrogen atom in position 1 (Scheme)[6] (Table 5).

The procedure described is a simple and efficient method for the preparation of both new 1-substituted and 1-unsubstituted 4-sulfonamido-1*H*-pyrazol-5(2*H*)-ones and, at the same time, represents an expeditious access to this class of widely substituted compounds as well as adding further proof of the utility of conjugated azoalkenes as building blocks in organic synthesis.

Aminocarbonyl azoalkenes **1a–b**, phenylaminocarbonyl azoalkenes **1c–d** and alkoxycarbonyl azoalkenes **1e–h** were prepared as previously reported.[7,8] *N*-Methyl-*p*-toluenesulfonamide **(2a)**, *o*-benzoic sulfimide (saccharin, **2b**) and *N'*-(2-thiazolyl)sulfanilamide **(2c)** are commercial materials (Aldrich, Acros or Lancaster) and were used without further purification. Melting points were determined in open capillary tubes with a Büchi (Tottoli) or Gallenkamp apparatus and are uncorrected. The products often decompose at melting point. IR spectra were obtained as film or nujol mull with a Perkin–Elmer 298 spectrophotometer. ^{1}H NMR spectra at 60 MHz were recorded on Varian EM 360 L and at 200 MHz on Bruker AC 200 spectrometers in DMSO-d_6. Chemical shifts (δ) are reported in ppm downfield from internal TMS and coupling constants (J) in Hz. Densitometric analysis was made with a Scanning Densitometer Shimadzu CS-9000. Macherey–Nagel precoated silica

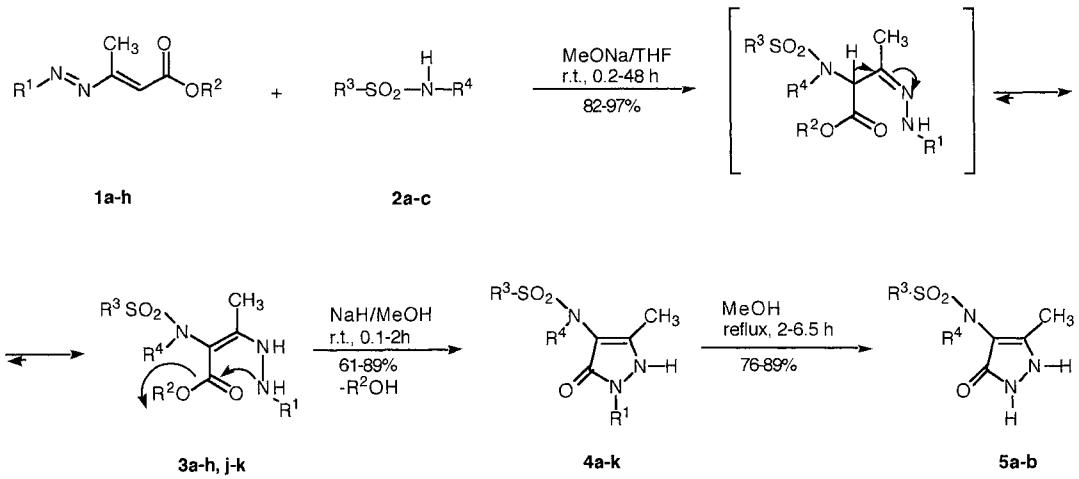
Table 1. Hydrazines **3a–h, j–k** Prepared

Reagents 1	2	Product[a] 3	Reaction Time (h)	Yield[b] (%)	mp[c] (°C)
1a	**2b**	**3a**	48	93	137–139
1b		**3b**	48	96	134–136
1c		**3c**	24	91	179–180
1d		**3d**	24	85	192–194
1e		**3e**	18	82	195–198
1f		**3f**	48	83	178–179
1h		**3g**	48	88	162–164
1a	**2c**	**3h**	2.0	96	196–198
1e		**3j**	0.2	97	160–162
1g		**3k**	0.5	85	172–173

[a] Satisfactory microanalyses obtained: C ± 0.35, H ± 0.30, N ± 0.30

[b] Yield of isolated product.

[c] Compounds **3a, c–e, g–j** were recrystallized from THF/pentane. Compounds **3b, f, k** were recrystallized from EtOAc/petroleum ether (bp 30–60 °C).



1a-h 2a-c 3a-h, j-k 4a-k 5a-b

1	R^1	R^2	2	R^3	R^4	3	R^1	R^2	R^3	R^4	4	R^1	R^3	R^4	5	R^3	R^4
a	$CONH_2$	Me	a	Me-Ph	Me	a	$CONH_2$	Me	O		a	$CONH_2$	Me-Ph	Me	a	Me-Ph	Me
b	$CONH_2$	Et	b	O		b	$CONH_2$	Et	O		b	CONHPh	Me-Ph	Me	b	O	
c	CONHPh	Me	c	H_2N-Ph-S-thiazole		c	CONHPh	Me	O		c	$CONH_2$	O				
d	CONHPh	Et				d	CONHPh	Et	O		d	CONHPh	O				
e	CO_2Me	Me				e	CO_2Me	Me	O		e	CO_2Me	O				
f	CO_2Bu-*t*	Me				f	CO_2Bu-*t*	Me	O		f	CO_2Bu-*t*	O				
g	CO_2Bu-*t*	Et				g	CO_2Et	Me	O		g	CO_2Et	O				
h	CO_2Et	Me				h	$CONH_2$	Me	H_2N-Ph-S-thiazole		h	$CONH_2$	H_2N-Ph-S-thiazole				
						j	CO_2Me	Me	H_2N-Ph-S-thiazole		i	CONHPh	H_2N-Ph-S-thiazole				
						k	CO_2Bu-*t*	Et	H_2N-Ph-S-thiazole		j	CO_2Me	H_2N-Ph-S-thiazole				
											k	CO_2Bu-*t*	H_2N-Ph-S-thiazole				

Scheme

gel SIL G-25 UV_{254} plates (0.25 mm) were employed for analytical TLC and silica gel Amicon LC 60 Å (35–70 mμ) for column chromatography. Petroleum ether used refers to bp 30–60 °C.

Hydrazines 3a–h, j–k; General Procedure:

To a magnetically stirred solution of conjugated azoalkenes **1a–h** (1.0 mmol) in THF (5.0 mL) was added dropwise a solution of sulfonamides **2b–c** in THF (5.0 mL) at r.t. To the mixture was added a catalytic amount of NaOMe (0.1 mmol). The typical red colour of conjugated azoalkenes disappeared and the hydrazines **3a–h**, **j–k** were formed (monitored by TLC) within 0.2–48 h in 82–97% yield (Table 1). After partial removal of the solvent in vacuo and subsequent addition of pentane, the products **3a**, **3c–e** and **3g–i** were collected by filtration as white powder in satisfactory purity. In the case of the products **3b**, **3f** and **3k**, after total evaporation of the solvent in vacuo, a white powder was obtained on addition of EtOAc/petroleum ether (1:3) to the residue.

1-Substituted 4-Sulfonamido-1*H*-pyrazol-5(2*H*)-ones 4a–k; General Procedure:

To a magnetically stirred solution of hydrazines **3a–h**, **j–k** (1.0 mmol) in MeOH (6.0 mL) was added NaH (24 mg, 1 mmol) at r.t. The conversion of the hydrazines **3a–h**, **j–k** to **4c–h** and **4j–k** occurred rapidly (monitored by TLC) within 0.1–2.0 h in 64–98% yield (Table 3). The products **4h**, **4j** and **4k** quickly precipitated from the reaction medium and were collected by filtration in satisfactory purity. The products **4c–g** were obtained in good purity by addition of CF_3CO_2H (2.0 mmol, 0.15 mL) to the reaction mixture, whence direct precipitation of **4c** and **4d** occurred. Compounds **4e–g** were collected after complete removal of the solvent in vacuo and subsequent addition of EtOAc/petroleum ether (1:3). Unlike the above-mentioned products, **4a** and **4b** were produced in one flask by reaction of conjugated azoalkenes **1a** and **1b** with *N*-methyl-*p*-toluenesulfonamide (**2a**), while the treatment of conjugated azoalkene **1d** with *N'*-(2-thiazolyl)sulfanilamide (**2c**) afforded in one pot the product **4i**. In both cases, after the disappearance of the starting conjugated azoalkenes **1a**, **1b**, and **1d** (monitored by TLC), the solvent was evaporated under reduced pressure and NaH was added to the residue in MeOH in an analogous way as above. The product **4i** was isolated by filtration as precipitate from MeOH. The reaction mixtures containing **4a** and **4b** were evaporated to dryness in vacuo and the residue dissolved in EtOAc (30 mL). The EtOAc layer was washed with 5% aq H_2SO_4 (3 × 30 mL) and with water (3 × 30 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude products **4a** and **4b** were purified by crystallization from EtOAc/petroleum ether.

Table 2. Spectral Data of Hydrazines **3a–j**

Product	IR (Nujol) ν (cm^{-1})	^1H NMR (200 MHz, DMSO-d_6/TMS)[a] δ, J (Hz)
3a	3450, 3310, 3160, 1730, 1670, 1570, 1370, 1325, 1300	1.96 (s, 3H, CH_3), 3.55 (s, 3H, OCH_3), 6.26 (s, 2H, NH_2), 8.01–8.32 (m, 4H_{arom}), 8.51 (s, 1H, NH), 10.28 (s, 1H, NH)
3b	3410, 3300, 3170, 1735, 1700, 1665, 1590, 1370, 1330, 1305	0.98 (t, J = 7, 3H, OCH_2CH_3), 1.94 (s, 3H, CH_3), 3.97 (q, J = 7, 2H, OCH_2CH_3), 6.26 (s, 2H, NH_2), 8.01–8.34 (m, 4H_{arom}), 8.41 (s, 1H, NH), 10.28 (s, 1H, NH)
3c	3260, 1740, 1650, 1590, 1540, 1370, 1330	2.01 (s, 3H, CH_3), 3.52 (s, 3H, OCH_3), 6.93–7.49 (m, 5H_{arom}), 7.99–8.33 (m, 4H_{arom}), 8.60 (s, 1H, NH), 9.18 (s, 1H, NH), 10.41 (s, 1H, NH)
3d	3260, 1730, 1650, 1595, 1550, 1370, 1335	1.01 (t, J = 7, 3H, OCH_2CH_3), 2.00 (s, 3H, CH_3), 3.99 (q, J = 7, 2H, OCH_2CH_3), 6.95–7.46 (m, 5H_{arom}), 8.03–8.31 (m, 4H_{arom}), 8.58 (s, 1H, NH), 9.19 (s, 1H, NH), 10.40 (s, 1H, NH)
3e	3260, 1740, 1720, 1655, 1580, 1370, 1340	1.95 (s, 3H, CH_3), 3.52 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 8.01–8.34 (m, 4H_{arom}), 9.56 (br s, 1H, NH), 10.34 (s, 1H, NH)
3f	3240, 1735, 1700, 1675, 1580, 1505, 1360, 1335	1.43 (s, 9H, O*t*-C_4H_9), 1.93 (s, 3H, CH_3), 3.51 (s, 3H, OCH_3), 8.01–8.34 (m, 4H_{arom}), 9.45 (br s, 1H, NH), 10.28 (s, 1H, NH)
3g	3260, 1730, 1660, 1590, 1370, 1335	1.20 (t, J = 7, 3H, CH_2CH_3), 1.94 (s, 3H, CH_3), 3.52 (s, 3H, CH_3), 4.11 (q, J = 7, 2H, OCH_2CH_3), 8.01–8.35 (m, 4H_{arom}), 9.65 (br s, 1H, NH), 10.33 (s, 1H, NH)
3h	3420, 3325, 3310, 3280, 1680, 1660, 1605, 1570, 1370, 1270	1.52, 1.83 (2s, 3H, CH_3), 3.44, 3.60 (2s, 3H, OCH_3), 5.84, 6.21 (2s, 2H, NH_2), 5.89 (s, 2H, NH_2), 6.54 (d, J = 8, 2H_{arom}), 6.80 (d, J = 4, 1H_{arom}), 7.09 (d, J = 4, 1H_{arom}), 7.37 (d, J = 8, 2H_{arom}), 8.41, 9.86 (2s, 1H, NH), 9.59 (s, 1H, NH)
3j	3460, 3345, 1735, 1665, 1605, 1590, 1370, 1280, 1250	1.49, 1.75 (2s, 3H, CH_3), 3.46 (s, 3H, OCH_3), 3.58, 3.62 (2s, 3H, OCH_3), 5.84 (s, 2H, NH_2), 6.54 (d, J = 8, 2H_{arom}), 6.81 (d, J = 4, 1H_{arom}), 7.16 (d, J = 4, 1H_{arom}), 7.38 (d, J = 8, 2H_{arom}), 9.53, 10.32 (br s and s, 1H, NH), 9.93 (s, 1H, NH)
3k	3460, 3350, 1725, 1660, 1635, 1590, 1370, 1295	0.94, 1.14 (2t, J = 7, 3H, OCH_2CH_3), 1.42 (s, 9H, O*t*-C_4H_9), 1.52, 1.80 (2s, 3H, CH_3), 3.83–4.13 (m, 2H, OCH_2CH_3), 5.83 (s, 2H, NH_2), 6.52 (d, J = 8, 2H_{arom}), 6.80 (d, J = 4, 1H_{arom}), 7.13 (d, J = 4, 1H_{arom}), 7.37 (d, J = 8, 2H_{arom}), 9.32, 10.00 (br s and s, 1H, NH), 9.87 (s, 1H, NH)

[a] NH-Protons are exchangeable with D_2O.

1-Unsubstituted 4-Sulfonamido-1*H*-pyrazol-5(2*H*)-ones 5a–b; General Procedure:

A solution of **4a–g** (1.0 mmol) in MeOH (10.0 mL) was refluxed for 2.0–6.5 h (Table 5) until complete conversion into **5a–b** was detected (monitored by TLC); yield 76–89%. After evaporation of the solvent in vacuo, the products **5a–b** were obtained by addition of EtOAc/petroleum ether (1:3) to the residue.

Table 3. Compounds **4a–k** Prepared

Reagents 1 or 3	2	Product[a] 4	Reaction Time (h)	Yield[b] (%)	mp[c] (°C)
1a	**2a**	**4a**[d]	0.1	69	167–169
1c	**2a**	**4b**[d]	0.1	61	173–175
3a		**4c**	1.0	64	297–299
3b		**4c**	0.5	65	297–299
3c		**4d**	0.5	71	303–304
3d		**4d**	0.1	71	303–304
3e		**4e**	0.5	89	263–265
3f		**4f**	0.5	69	303–305
3g		**4g**	0.3	69	279–281
3h		**4h**	0.1	98	305–307
1d	**2c**	**4i**[d]	2.0	82	312–314
3j		**4j**	0.2	92	207–210
3k		**4k**	2.0	98	204–206

[a] Satisfactory microanalyses obtained: C ± 0.40, H ± 0.35, N ± 0.30.

[b] Yield of isolated products **4a, b, d** was based on **1** and **4c–h, j, k** on **3**.

[c] Compounds **4a, b, e–g** were recrystallized from EtOAc/petroleum ether and **4c, d, h–k** from MeOH.

[d] Products obtained without isolation of intermediate adducts.

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Table 4. Spectral Data of **4a–k**

Compound	IR (Nujol) ν (cm^{-1})	^1H NMR (200 MHz, DMSO-d_6/TMS)[a]
4a	3390, 3275, 3140, 1735, 1635, 1560, 1370, 1340	2.10 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.01 (s, 3H, CH_3), 7.36 (d, J = 8, 2 H_{arom}), 7.67 (d, J = 8, 2 H_{arom}), 7.77, 8.04 (2s, 2H, NH_2), 11.18 (br s, 1H, NH)
4b	3190, 1695, 1670, 1600, 1570, 1370, 1320	2.16 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.06 (s, 3H, CH_3), 7.11–7.41 (m, 5 H_{arom}), 7.51 (d, J = 8, 2 H_{arom}), 7.71 (d, J = 8, 2 H_{arom}), 10.93 (s, 1H, NH), 12.11 (br s, 1H, NH)
4c	3360, 3220, 3100, 1745, 1725, 1660, 1570, 1375, 1335	2.18 (s, 3H, CH_3), 8.04–8.40 (m, 4 H_{arom} and 2H, NH_2), 13.52 (br s, 1H, NH)
4d	3450, 3170, 1735, 1710, 1670, 1605, 1560, 1370, 1330	2.24 (s, 3H, CH_3), 7.13–7.58 (m, 5 H_{arom}), 8.02–8.42 (m, 4 H_{arom}), 10.98 (s, 1H, NH), 13.69 (br s, 1H, NH)
4e	3440, 1740, 1670, 1580, 1370, 1330	2.03 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 7.98–8.35 (m, 4 H_{arom}), 12.92 (br s, 1H, NH)
4f	3440, 1750, 1660, 1580, 1370, 1335, 1295	1.55 (s, 9H, O*t*-C_4H_9), 2.13 (s, 3H, CH_3), 8.01–8.39 (m, 4 H_{arom}), 12.88 (br s, 1H, NH)
4g	3440, 1745, 1675, 1580, 1370, 1335, 1290	1.32 (t, J = 7, 3H, OCH_2CH_3), 2.14 (s, 3H, CH_3), 4.38 (q, J = 7, 2H, OCH_2CH_3), 8.04–8.39 (m, 4 H_{arom}), 12.98 (br s, 1H, NH)
4h	3540, 3440, 3370, 1695, 1610, 1590, 1370, 1280	1.68 (s, 3H, CH_3), 5.82 (s, 2H, NH_2), 6.53 (d, J = 8, 2 H_{arom}), 6.76 (d, J = 4, 1 H_{arom}), 6.99, 9.01 (2s, 2H, NH_2), 7.05 (d, J = 4, 1 H_{arom}), 7.40 (d, J = 8, 2 H_{arom}), 12.52 (br s, 1H, NH)
4i	3530, 3440, 3360, 3220, 1690, 1590, 1560, 1370, 1280	1.73 (s 3H, CH_3), 5.84 (s, 2H, NH_2), 6.56 (d, J = 8, 2 H_{arom}), 6.80 (d, J = 4, 1 H_{arom}), 7.00–7.53 (m, 8 H_{arom}), 12.43 (s, 1H, NH), 12.90 (br s, 1H, NH)
4j	3460, 3370, 3230, 1720, 1630, 1590, 1370, 1340, 1300	1.62 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 5.83 (s, 2H, NH_2), 6.54 (d, J = 8, 2 H_{arom}), 6.74 (d, J = 4, 1 H_{arom}), 7.00 (d, J = 4, 1 H_{arom}), 7.39 (d, J = 8, 2 H_{arom}), 10.01 (br s, 1H, NH)
4k	3570, 3520, 3440, 3340, 1730, 1640, 1620, 1595, 1370, 1340, 1260	1.48 (s, 9H, O*t*-C_4H_9), 1.61 (s, 3H, CH_3), 5.82 (s, 2H, NH_2), 6.54 (d, J = 8, 2 H_{arom}), 6.74 (d, J = 4, 1 H_{arom}), 6.98 (d, J = 4, 1 H_{arom}), 7.40 (d, J = 8, 2 H_{arom}), 9.80 (br s, 1H, NH)

[a] NH-Protons are exchangeable with D_2O.

Table 5. Compounds **5a, b** Prepared

Reagent **4**	Product[a] **5**	Reaction Time (h)	Yield[b] (%)	mp (°C)	IR (Nujol) ν (cm^{-1})	^1H NMR (200 MHz, DMSO-d_6/TMS)[c] δ, J (Hz)
4a	**5a**	5.5	83	208–209	3440, 3180, 1605, 1570, 1370, 1335	1.94 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.01 (s, 3H, CH_3), 7.34 (d, J = 8, 2 H_{arom}), 7.55 (d, J = 8, 2 H_{arom}), 10.49 (br s, 2H, 2NH)
4b	**5a**	4.0	89			
4c	**5b**	5.5	77	302–303	3340, 1735, 1720, 1550, 1370, 1335	2.09 (s, 3H, CH_3), 8.01–8.36 (m, 4 H_{arom}), 11.00 (br s, 2H, 2NH)
4d	**5b**	2.0	79			
4e	**5b**	3.0	76			
4f	**5b**	6.5	76			
4g	**5b**	5.5	76			

[a] Satisfactory microanalyses obtained: C ± 0.40, H ± 0.35, N ± 0.30.
[b] Yield of isolated products **5** based on **4**. Recrystallized from EtOAc/petroleum ether.
[c] NH-Protons are exchangeable with D_2O.